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INVITED NARRATIVE REVIEW

COVID-19 and cervical lymphadenopathy

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Abstract

COVID-19 has brought a number of diseases secondary to viral infection, and there have been several reports on clinical manifestations related to vaccination. One of the effects reported in the literature, either related to the disease or to the vaccines, is the occurrence of cervical lymphadenopathy, which can result in a misleading differential diagnosis of malignant neoplasms. It is important that the specialist be aware of this differential diagnosis for an accurate management of cases.

Keywords: COVID-19; COVID-19 vaccination; lymphadenopathy.

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Cervical lymphadenopathy is not often observed in presentations of acute coronavirus disease (COVID-19) in children or adults, even in cases with severe manifestations. There are few reports of cervical lymphadenopathy associated with COVID-19 infection in the literature[1], with level II lymph nodes as the most commonly affected. Level II lymph nodes are responsible to drain the pharynx, which is one of the sites where COVID-19 causes inflammation, with frequent symptoms of tonsillitis or nasopharyngitis. This inflammation leads to a local immune response, with consequent involvement of not only of the cervical lymph nodes, but also of the parotid lymph nodes, which also explains the increase in cases of acute parotiditis[2,3].

The outbreak of the COVID-19 pandemic brought the need for knowledge about specific events in all population segments[4-6]. Symptoms of acute COVID-19 are similar in children and adults, but the frequency of findings varies[7]. Acute cases seem to be milder in children than in adults, but severe cases are also observed in the pediatric population[8]. A systematic review of the literature conducted in 2020 revealed that the proportion of asymptomatic cases in the population aged ≤20 years ranges from 15 to 42%[9]. The reasons why COVID-19 is less severe in children than in adults are still unclear[10].

Some studies do not mention the presence of enlarged cervical lymph nodes among the signs and symptoms of acute COVID-19 in children[10]; however, these are present in 6-16% of cases that progress to pediatric multisystem inflammatory syndrome (MIS-C) associated with COVID-19, associated or not with Kawasaki disease (KD)[11,12].

MIS-C occurs in <1% of children with confirmed COVID-19 infection, and is even rarer in adults[11,13-15]. The time elapsed from acute infection to MIS-C

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symptom onset (3-4 weeks) is the same to onset of acquired immunity, suggesting that this is a post-infectious complication[16,17].

Most cases of MIS-C associated or not with KD occur in previously healthy children, whereas severe acute COVID-19 is more frequent in those with comorbidities[12]. MIS-C alone mainly affects older children and adolescents and those of African or Hispanic origin; in contrast, classical KD usually affects younger children and has a higher incidence among Asian descent[10,18,19].

The main clinical manifestations of MIS-C and KD include fever, rashes, mucous membrane involvement, conjunctivitis, edema/erythema of the hands and feet, and cervical lymphadenopathy, with the last present in 30-70% of MIS-C cases and in 50-70% of KD patients[19]. Gastrointestinal symptoms, shock, and coagulopathy are common in MIS-C patients, but are not common in classic KD[19].

A systematic review designed to identify the clinical features of pediatric COVID-19 evaluated 46 case reports and case series with a total of 112 children, and found that only 3 (2.7%) had cervical lymphadenopathy and all were aged 1-10 years (4.9% of this age group)[14]. Lymphadenopathy has been identified upon physical examination and after infection[15,16].

A prospective multicenter observational cohort study published in August 2020 analyzed the clinical characteristics of 615 children aged <19 years admitted to 136 hospitals in the United Kingdom with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), and found that 20% of them had MIS-C and presented enlarged lymph nodes[18]. However, there are no studies relating the presence of cervical lymphadenopathy as a single prognostic predictor.

Although the literature shows a relationship between COVID-19 vaccines and the onset of cervical lymphadenopathy, the study samples are restricted to adults. Analysis of the side effects of vaccination in children does not mention cervical lymph node involvement[20].

Post-vaccination lymphadenopathy has been documented in several types of vaccines, such as in those used against the influenza virus and the human papillomavirus (HPV)[21,22]. This reaction can occur in response to all types of COVID-19 vaccines. Upon muscle injection, the vaccine is transported to regional lymph nodes and, in some cases, to the nearest lymphatic chains, with subsequent activation of T and B cells in these lymph nodes[23]. In these cases, lymphadenopathy usually occurs in the supraclavicular region (level IV) as a result of drainage chains originating from the axillary region. Axillary lymphadenopathy is considered the second most frequent cause of local reaction to messenger RNA vaccines[24].

Complementary imaging exams may show changes, and lead to suspicion of neoplasms in patients with vaccination-induced lymphadenopathy. Positron Emission Tomography and Computed Tomography (PET-CT) may show increased fluorodeoxyglucose uptake into lymph nodes, resulting in a misleading diagnosis, especially if there is no information about recent vaccination history. Ultrasound (US) should be considered as an effective test that can assist with differential diagnosis, with the advantage of having a lower cost. The finding of a preserved fatty hilum is a sign of lymph node benignity[24-26].

Some authors have proposed that routine breast cancer screening tests be performed before vaccination, or between 4 and 6 weeks after the second dose, because of the risk of emergence of enlarged lymph nodes, which may cause diagnostic doubt[25,26].

Fine-needle aspiration (FNA), or core biopsy, may aid in diagnosis. Findings reported by pathologists on lymphadenopathy caused by vaccination include a reactive pattern with follicular hyperplasia and prominent elements in the germinal center, including lymphoid-histiocytic cell and macrophage aggregation. Another important aspect of this analysis is the risk of a false positive diagnosis of lymphoproliferative disease due to increased population of activated lymphoid cells, and it is fundamental that the surgeon inform the pathologist of the disease or vaccination history[27].

It is essential that the specialist be aware of COVID-19 and all its clinical repercussions, which can be related to both infection and vaccination. The patient's history and clinical examination, as well as good quality US, are essential to avoid unnecessary invasive treatments, as these conditions present gradual recovery, and it may take 3 to 4 weeks for spontaneous remission of lymphadenopathy to occur[28].

Based on the data available to date, we do not recommend the use of COVID-19 diagnostic tests in the routine investigation of cervical lymphadenopathy in patients who do not meet the criteria for MIS-C.

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